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1. Your reference	JNR/DAB/PB60589P
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3. Full name, address and postcode of the or of each applicant *(underline all surnames)*	Glaxo Group Limited Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, Great Britain
Patents ADP number *(if you know it)* 473587003	
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Description	23
Claim(s)	1
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Method for predicting deposition of inhaled medicament at the lung

Technical field

The present invention relates to a method for predicting the deposition of inhaled medicament in the throat of a patient. The method is particularly useful in predicting the likelihood of throat deposition of medicament, wherein the medicament is arranged for delivery to the patient's lung of a patient by way of an inhaler-type dispenser device.

Background to the invention

The use of inhaler devices in the administration of medicaments, for example in bronchodilation therapy is well known. Such devices generally comprise a body or housing within which a medicament carrier is located. Known inhaler devices include those in which the medicament is in dry powder form, including those in which the medicament carrier is a blister strip containing a number of discrete doses of powdered medicament. Such devices usually contain a mechanism of accessing these doses, usually comprising either piercing means or means to peel a lid sheet away from a base sheet. The powdered medicament can then be accessed and inhaled. Other known devices include those in which the medicament is delivered in aerosol form, including the well known metered dose inhaler (MDI) delivery devices. Liquid-based inhaler devices are also known.

Considerable research effort is directed towards the design of new and improved inhaler devices. One important measure of performance of such inhaler devices is the ability to deliver inhaled medicament to the lung of a patient. It is relatively difficult and expensive to conduct performance tests relating to delivery of medicament to the lung performance on live patients (i.e. *in vivo*). A number of

standard *in vitro* test methods have therefore been developed in order that inhaler performance may be assessed in the laboratory. Known laboratory test methods included those utilising a pump operated under defined (e.g. standardized) flow conditions and coupled to any of a Marple Miller Impactor (MMI); Twin Impinger (BP); Multi-Stage Liquid Impinger (MLSI); or Andersen Impactor (AI). Other known laboratory test methods utilise apparatus that more or less mimics the action of an inhaling patient. Thus, the inhaler device communicates with an artificial 'mouth' leading respectively to an artificial 'throat', 'respiratory tract' and 'lungs'. The apparatus is arranged such that positive and negative vacuum may be applied in order to simulate the breathing action of a patient. Known apparatus of this sort include the electronic lung.

It is known from both *in vivo* and the above *in vitro* assessments that a significant proportion of medicament inhaled from an inhaler device deposits in the upper respiratory tract, which includes the mouth and throat of a patient, and therefore never reaches its primary therapeutic delivery target point at the lung. Considerable effort has therefore been directed towards understanding pre-lung deposition to enable the design of improved *in vitro* laboratory performance testing apparatus, in particular such apparatus that more effectively simulates what happens *in vivo*.

It has been appreciated that variations in mouth, throat and respiratory tract geometries and dimensions between different patients can affect the tendency for undesirable pre-lung deposition of inhaled medicament. The variation can be particularly broad between paediatric and adult patient groups and even between adults of large build versus smaller adults. For effective simulation of *in* vivo performance, it is therefore desirable to tailor laboratory methods and apparatus for pre-lung throat deposition to take account of the above-described variation in mouth, throat and respiratory tract geometries and dimensions between different patients. Existing methods for measuring patient mouth, throat and respiratory tract geometries, which rely on either assessment of cadavers or on the use of Magnetic Resonance Imaging (MRI) or Computated Tomography (CT) of the throats of live

patents, are however expensive and time-consuming and therefore somewhat impractical for commercial use with large patient samples.

The Applicant has now devised a method of assessing pre-lung deposition that both takes account of diverse mouth, throat and respiratory tract geometries and dimensions across patient sample groups and is readily applicable, at reasonable cost, to large patient sample groups. The method relies on the use of acoustic imaging (e.g. acoustic reflection imaging) to map the internal geometry of the mouth, throat and upper respiratory tract of each patient in the sample group. The so-mapped patient geometries are then matched to existing patient geometries derived using current (typically expensive, and time-consuming) methods for which pre-lung deposition data is available or to bent-pipe models to enable pre-lung deposition patterns to be predicted for the acoustically mapped geometries.

The Applicant has also found that pre-lung deposition may be effectively correlated with one or more key internal parameters of a patient's throat. The above-described method may therefore be further simplified by acoustic measurement of these key geometric parameters across the patient sample groups.

PCT Patent Application No. WO 01/74247 describes a method of employing real-time Magnetic Resonance Imaging (MRI) to investigate the effect of patient air way structures on the oral inhalation of a respiratory medicament.

It is an object of the present invention to provide a method for predicting the extent of pre-lung deposition of medicament delivered orally by an inhaler device for patients with a variety of different throat sizes.

It is a further object of the present invention to provide improved laboratory testing apparatus for use in predicting pre-lung deposition of medicament delivered by an inhaler device.

Summary of the invention

According to one aspect of the invention there is provided a method for predicting the tendency of inhaled particles to deposit within a first patient's throat when said particles are inhaled through an airway defined by said throat, said method comprising

determining at least one internal physical parameter of said airway defined by the first throat by means of acoustic imaging of the airway defined by the first throat; and

matching said at least one internal physical parameter of the airway of the first throat with a dataset comprising pre-determined data relating to the corresponding internal physical parameter for the throat of at least one other patient,

wherein said dataset also comprises pre-determined data relating to the tendency of said inhaled particles to deposit within at least one other patient's throat, and said matching thereby enables prediction of the tendency for the inhaled particles to deposit within the first patient's throat.

There is provided a method for predicting the tendency of inhaled particles to deposit within a first patient's throat. That is to say, the method enables prediction of the tendency of particles to deposit within a first patient's throat when said particles are orally inhaled through said first throat.

The method is suitable for the predictive assessment of particle deposition within a patient's throat to which particulate product is delivered by a delivery system. In general terms, the method is suitable for use in predictive assessments where both throat internal physical parameter data and throat particle deposition data exists for at least one other patient (e.g. in an existing patient database).

The method also enables prediction of lung deposition of the particles, which may be obtained by subtracting the number, mass (or %) of particles deposited on the throat from the total number of particles (i.e. initially 100%) inhaled by the patient.

Suitable particles typically comprise particles of medicament either in the form of a formulated medicated product or as pure drug or alternatively, the particles may comprise placebo. Suitably, the particles are deliverable by means of an inhaler-type delivery device (e.g. a dry powder inhaler device for the delivery of dry powdered medicament or medicament formulation).

In the method, at least one internal physical parameter of the airway defined by the throat of the first patient is determined by means of acoustic imaging (e.g. acoustic reflection imaging) of the airway defined by that first patient's throat.

The term throat herein is essentially used to mean that part of the human body (or suitable laboratory model thereof) encountered by particles delivered to a mouth for inhaled transport to the lung that occurs prior to the lung. As used herein, the term throat therefore encompasses the mouth cavity, pharynx, epiglottis, larynx and trachea and any defined separate part thereof. In one aspect, the throat is taken to comprise that part of the mouth cavity and respiratory tract down to the patient's fifth vertebrae.

The term throat airway herein is used to mean that airway (or airpath) defined by the inner walls of the throat. It will be appreciated that throat deposition potentially occurs on said throat walls and also on any structures within the airway when particles are drawn through the airway defined thereby.

Suitable physical parameters that may be used to define the airway defined by the throat include the throat volume, area of a suitable cross-section (e.g. that taken in a coronal plane) and length of the throat (e.g. taken in the central sagittal plane).

The at least one internal physical parameter of the airway defined by the throat of the first patient is determined by acoustic imaging thereof such as by an acoustic imaging method using acoustic reflection. A suitable method of acoustic reflection imaging involves the use of an acoustic pharyngometry apparatus. One such suitable apparatus is sold by Hood Laboratories of 575 Washington St, Pembroke, MA 02359, United States of America under the trade name Eccovision and described in the Operating Manual therefor.

Suitable apparatus for acoustic pharyngometry are further described in PCT Patent Application No. WO 94/09700 also in the name of Hood Laboratories and comprise a hand-held acoustic imaging head which is rugged and entirely hand supportable and operable by an operator, throughout an imaging procedure, which head comprises;

A. a rugged hand-holdable housing having
   1. an elongate body, defined by
      (a) a top end;
      (b) a base end;
      (c) an outer wall extending between the top end and the base end; and
      (d) an internal chamber;
   2. an aperture through the housing top end, providing fluid communication between the internal chamber and the outside of the housing; and
   3. a shape and configuration of the outer wall facilitating gripping of the housing with a human hand;

B. an acoustic pipe for transmitting acoustical energy and receiving the reflected acoustical energy, mounted in the aperture, said pipe having a first end within the chamber and an open second end outside of the housing, said second end of the acoustic pipe being adapted for connection of the acoustic pipe to an orifice leading into the respiratory tract;

C. a launching transducer mounted in the chamber and coupled to the first end of the acoustic tube, for launching acoustical energy into the acoustic pipe, propagating an incident wave out of the open second end;

D. at least one acoustic pressure wave sensing transducer mounted on the acoustic pipe at a location between the first and second ends of the acoustic pipe, for sensing reflections of the incident wave, received back in the acoustic tube through the open second end and generating a signal; and

E. means at least partially within the chamber, connected to the acoustic wave sensing transducer, for transmission of signals transduced, to processor means for processing said signals into a processor output signal characteristic of the morphology of a site within the respiratory tract of the patient.

Acoustic reflection methods and apparatus have also been described in the following journal articles:

J Appl Physiol. 1984 Sep;57(3):777-87. Reproducibility and accuracy of airway area by acoustic reflection. Brooks LJ, Castile RG, Glass GM, Griscom NT, Wohl ME, Fredberg JJ.

Am Rev Respir Dis. 1987 Feb;135(2):392-5. Airway area by acoustic response measurements and computerized tomography. D'Urzo AD, Lawson VG, Vassal KP, Rebuck AS, Slutsky AS, Hoffstein V.

Eur Respir J. 1991 May;4(5):602-11. The acoustic reflection technique for non-invasive assessment of upper airway area. Hoffstein V, Fredberg JJ.

Ann Biomed Eng. 1995 Jan-Feb;23(1):85-94. Measurement of upper airway movement by acoustic reflection. Zhou Y, Daubenspeck JA.

J Appl Physiol. 1994 May;76(5):2234-40. Pulmonary airway area by the two-microphone acoustic reflection method. Louis B, Glass GM, Fredberg JJ.

Physiol Meas. 1993 May;14(2):157-69. Acoustic reflectometry for airway measurements in man: implementation and validation. Marshall I, Maran NJ, Martin S, Jan MA, Rimmington JE, Best JJ, Drummond GB, Douglas NJ.

J Appl Physiol 2000 Apr;88(4):1457-66. A new nasal acoustic reflection technique to estimate pharyngeal cross-sectional area during sleep. Huang J, Ital N, Hoshiba T, Fukanaga T, Yamanouchi K, Toga H, Takahashi K, Ohya N.

The method provided herein involves matching said at least one internal physical parameter of the airway defined by the first patient's throat and determined by acoustic imaging of that airway with a dataset comprising pre-determined data relating to the corresponding internal physical parameter for the (airways defined by the) throats of each of plural other patients. That is to say, in a pre-step, data relating to the corresponding internal physical parameter is collected for the throat of at least one other patient and that data collated as a dataset to which comparison for matching purposes with the at least one internal physical parameter of the first patient's throat may be made.

The internal physical parameter data of the pre-determined dataset may be collected from the airway defined by the throat of each of the at least one other patient by any suitable method.

In one aspect, the pre-determined dataset comprises internal physical parameter data for the throats of plural other patients, for example at least ten, preferably at least twenty, more preferably as large a sample as possible of other patients.

In another aspect, the data is collected by study of just one other patient by varying the particle size of the particles inhaled and/or the inspiratory flow rate for that patient's throat.

In one aspect, data is collected by use of Magnetic Resonance Imaging (MRI) of the throat airways particular to the plural other patients. Such MRI techniques are known to be expensive and time-consuming, so for commercial reasons it may be necessary to limit the dataset to a relatively small number of patients, but not so small that the quality (i.e. for matching purposes) of the dataset is compromised.

References describing MRI imaging of patient throats include:

3D reconstruction of the upper airway during inhalation from drug delivery system using MRI: Ehtezazi T, Horsfield MA, Barry P and O Callaghan CO, (2000) Proceedings of Drug Delivery to the lungs XI, pages 90-93;

Lung Air spaces: MR Imaging evaluation with hyperpolarized 3He gas, de Lange EE, Mugler JP III, Brookeman JR, Knight-Scott J, Truwit JD, Teates CD, Daniel TM, Bogorad PL, Cates GD. Radiology, 1999, 210 (3), pages 851-857;

McRobbie DW, Pritchard S, Quest R (2003) Studies of the human oropharyngeal airspaces using magnetic resonance imaging I. Validation of a three-dimensional MRI method for producing ex vivo virtual and physical casts of the oropharyngeal airways during inspiration. J Aerosol Medicine 16: 399-413;

McRobbie DW, Pritchard SE, Quest RA. Volumetric studies of the oropharyngeal airways by 3D MRI. International Society for Aerosols in Medicine, 13th International Congress; 17-21 Sep 2001; and

McRobbie D.W., Quest R.A., Pritchard S. (2000) "Pulse Sequences for Respiratory Gated MR Virtual Bronchoscopy", International Society for Megnetic Resonance in Medicine, 8h ann. Mtg, Denver no. 1749.

In another aspect, the data is collected by use of bent-pipe throat models with suitably selected patient throat dimensions.

The pre-determined dataset suitably also comprises data relating to the particle size distribution of the particulate product to be inhaled. Aerosol compositions, for example, typically have a particular particle size distribution.

The pre-determined dataset also comprises data relating to the tendency of said inhaled particles to deposit within each of said at least one other patient's throat. That is to say, for each patient the dataset comprises at least a first data point relating to the at least one internal physical parameter relevant to that patient's throat airway and at least a second data-point relating to the tendency of inhaled particles to deposit within that patient's throats on inhalation of particles through that patient's throat.

Patient throat deposition data is typically obtained by making a model reconstruction of the patient's throat based upon dimensional and geometric information obtained by previous measurements. A particulate sample product of known composition and physical characterisation is then caused to be inhaled through the reconstructed throat. Deposition of particulate material in the throat is assessed using a method such as gamma scintigraphy or gravimetry or other methods known in the art.

In the method, the at least one internal physical parameter of the first patient's throat airway is matched with the pre-determined dataset and that matching enables prediction of the tendency for the inhaled particles to deposit within the first patient's throat.

Any suitable matching process is envisaged including those relying on statistical methods such as curve-fitting methods, as are known in the art.

According to another aspect of the invention there is provided a method for predicting the tendency of inhaled particles to deposit within an airway defined by a first patient's throat, said method comprising

(a) assembling a dataset comprising data relevant to each of plural patients by

(i) determining at least one internal physical parameter of the airway defined by the throat of at least one other patient; and

(ii) determining the tendency of inhaled particles to deposit within the throat of said at least one other patient

(b) determining at least one internal physical parameter of the airway defined by the first throat by means of acoustic imaging of the airway defined by the throat; and

(c) matching said at least one internal physical parameter of the airway defined by the first throat with said dataset,

wherein reference to said matching thereby enables prediction of the tendency for the inhaled particles to deposit within the first patient's throat.

It will be appreciated that in this aspect, the step of assembling a dataset comprising physical parameter and particle deposition data relevant to the at least one other patient essentially comprises a pre-step whereby a reference dataset is compiled for use in the later matching with the at least one internal physical parameter of the airway defined by the first throat to enable the first throat's tendency for inhaled particle deposition to be predicted.

The Applicant has found that the methods described herein are particularly suitable for assessment of throat deposition where the medicament to be inhaled is supplied from a passive delivery system, in which the principal (or indeed, total) source of energy to draw the medicament into the lung is supplied by the patient's breath. Passive delivery tends to be employed in dry powder delivery devices wherein the patient's breath is harnessed to aerosolise the dry powder dose. Passive delivery is also typically the mechanism in nebuliser type delivery systems, in which the medicament to be inhaled in supplied as a relatively passive cloud. Both of these passive systems contrast with the well-known metered dose inhaler ('puffer') type device in which an energised puff of aerosol cloud is supplied for inhalation.

The methods described herein are also suitable for assessment of throat deposition where the medicament to be inhaled is supplied from a more active delivery system, in which the inhaler provides initial energy (e.g. kinetic energy) to the medicament to be inhaled (e.g. release of aerosolised medicament from a metered dose inhaler). Further pre-steps may be involved when the methods are so-employed such as the creation of a dataset specific to the particular active delivery system (e.g. particular to MDIs).

It will be appreciated that aspects of the method herein, particularly data processing and matching aspects, are susceptible to being carried out by a suitably programmed computer.

Thus, according to a further aspect of the present invention, at least aspects of the method described above are implemented in the form of computer software. The software may comprise a computer program comprising program code means for, when executed on a computer, instructing a computer to perform some or all of the steps of the method. The software may also comprise a computer program product comprising a computer readable recording medium having recorded thereon a computer program comprising code means for, when executed on a computer, instructing said computer to perform some or all of the steps of the method.

Brief Description of the Drawings

The invention will now be described with reference to the accompanying drawings in which:

Figure 1 shows a cross-sectional view of a patient's head and upper respiratory tract taken along the sagittal plane;

Figure 2 shows data arising from the use of an acoustic reflection imaging device illustrating area (in cm^2) versus distance (in cm) for a typical patient throat; and

Figure 3 shows a plot of throat deposition (% delivered dose) versus throat volume (in mm^3) when a nebulised product is inhaled through a model human throat.

Detailed Description of the Drawings

Figure 1 shows a cross-sectional view of a patient's head and upper respiratory tract taken along the sagittal plane, that is to say the plane that defines the left hand side of the patient's body from the right hand side thereof.

In more detail, Figure 1 respectively shows the nasal cavity 1, hard palate 2, oral cavity 3, tongue 4, nasopharynx 5, soft palate 6, uvula 7, pharynx 8, epiglottis 9, laryngo-pharynx 10, oesophagus 11 and laryngeal cavity 12 of the patient. Also shown is central line 14 of the throat airway of the patient in the sagittal plane. In accord with the method herein, the path length (L) of the throat of the patient is measured along the central line 14.

Figure 2 shows data arising from the use of an acoustic reflection imaging device illustrating area (in cm^2) versus distance (in cm) for a typical patient throat. Anatomical landmarks have been included for clarity. The acoustic wave behaves much like a sonar and the walls and structures of the throat airways cause reflections which when interpreted provide cross-sectional area data along the throat distance of interest.

Figure 3 shows the percentage (%) of nebulized material deposited in plural throat models of different volumes demonstrating that the at least one dimension of the single throat can be used to provides an estimate of throat deposition for a particular inhaled particulate product.

In an illustrative method herein, throat physical parameter data was collected from the throats of an initial sample of twenty patients. The sample group was selected to comprise patients of different builds (i.e. large and small adults) to give a good range of throat sizes. The physical parameter data collected for each patient included amongst others: the volume of the airway defined by the patient throat; the cross-section area of that airway measured in various planes including the sagittal, coronal and axial; and length of that airway also measured in the central sagittal plane. The data was collected by use of Magnetic Resonance Imaging (MRI) of the throat airway of each patient in the sample group.

Throat deposition data was also collected for the same initial patient sample by requiring a defined particle sample to be inhaled through a model airway defined by and constructed according to the physical throat parameters of each patient under measurable inhalation flow conditions.

A reference database was thus, assembled in computerised form to comprise throat physical parameter and corresponding throat deposition data for each patient in the sample group. Using appropriate plots, the throat deposition data was plotted against the throat physical parameter data to give reference curves that might be used in a

predictive sense (e.g. to predict throat deposition for a new patient for whom suitable throat physical parameter data is known).

A further (i.e. new) patient was then selected for whom it was desired to predict the tendency of the defined particle sample to deposit within their throat. The airway defined by the throat of this patient was then mapped using reflection acoustic imaging such that physical parameter data was obtained corresponding to the volume of the airway defined by the patient throat; the cross-section area of that airway measured in that sagittal plane; and length of that airway also measured in the central sagittal plane.

In more detail, the acoustic reflection imaging technique comprised use of the Acoustic Pharyngometry apparatus sold by Hood Laboratories of 575 Washington St, Pembroke, MA 02359, United States of America under the trade name Eccovision. The apparatus was used in accord with the Operating Manual provided therewith, which involves taking acoustic measurements of throat characteristics during oral inhalation by the patient.

The physical parameter data defining the airway of the new patient was then cross-referenced with the data of the reference database. By matching of the new patient physical parameter data with the data of the reference database (e.g. by fitting to appropriate reference curves) the tendency for particle deposition to occur at the throat of the new patient was predicted.

The method of the present invention is suitable for use in the assessment of inhalation-type medicament dispenser devices, such as those suitable for the delivery of medicament for the treatment of respiratory disorders such as asthma and chronic obstructive pulmonary disease (COPD), bronchitis and chest infections and for the systemic treatment of insulin-dependent diabetes.

Appropriate medicaments may thus be selected from, for example, analgesics, e.g., codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g., diltiazem; antiallergics, e.g., cromoglycate (e.g. as the sodium salt), ketotifen or nedocromil (e.g. as the sodium salt); antiinfectives e.g., cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g., methapyrilene; anti- inflammatories, e.g., beclomethasone (e.g. as the dipropionate ester), fluticasone (e.g. as the propionate ester), flunisolide, budesonide, rofleponide, mometasone e.g. as the furoate ester), ciclesonide, triamcinolone (e.g. as the acetonide) or 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17β-carbothioic acid S-(2-oxo-tetrahydro-furan-3-yl) ester; antitussives, e.g., noscapine; bronchodilators, e.g., albuterol (e.g. as free base or sulphate), salmeterol (e.g. as xinafoate), ephedrine, adrenaline, fenoterol (e.g. as hydrobromide), formoterol (e.g. as fumarate), isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol (e.g. as acetate), reproterol (e.g. as hydrochloride), rimiterol, terbutaline (e.g. as sulphate), isoetharine, tulobuterol or 4-hydroxy-7-[2-[[2-[[3-(2-phenylethoxy)propyl]sulfonyl]ethyl]amino]ethyl-2(3H)-benzothiazolone; adenosine 2a agonists, e.g. 2R,3R,4S,5R)-2-[6-Amino-2-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(2-ethyl-2H-tetrazol-5-yl)-tetrahydro-furan-3,4-diol (e.g. as maleate); α_4 integrin inhibitors e.g. (2S)-3-[4-({[4-(aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-[((2S)-4-methyl-2-{[2-(2-methylphenoxy) acetyl]amino}pentanoyl)amino] propanoic acid (e.g. as free acid or potassium salt), diuretics, e.g., amiloride; anticholinergics, e.g., ipratropium (e.g. as bromide), tiotropium, atropine or oxitropium; hormones, e.g., cortisone, hydrocortisone or prednisolone; xanthines, e.g., aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; therapeutic proteins and peptides, e.g., insulin or glucagon; vaccines, diagnostics, and gene therapies. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts, (e.g., as alkali metal or amine salts or as acid addition salts) or as esters (e.g., lower alkyl esters) or as solvates (e.g., hydrates) to optimise the activity and/or stability of the medicament.

Suitable medicament components for the treatment of respiratory disorders are particularly selected from the group consisting of anti-inflammatory agents (for example a corticosteroid or an NSAID), anticholinergic agents (for example, an M_1, M_2, M_1/M_2 or M_3 receptor antagonist), other β_2-adrenoreceptor agonists, antiinfective agents (e.g. an antibiotic or an antiviral), antihistamines, and mixtures thereof.

Suitable anti-inflammatory agents include corticosteroids and NSAIDs. Suitable corticosteroids which may be used in combination with the compounds of the invention are those oral and inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity. Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17β-carbothioic acid *S*-(2-oxo-tetrahydro-furan-3S-yl) ester, beclomethasone esters (e.g. the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone acetonide, rofleponide, ciclesonide, butixocort propionate, RPR-106541, and ST-126. Preferred corticosteroids include fluticasone propionate, 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester and 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, more preferably 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester.

Suitable NSAIDs include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine

antagonists (e.g. chemokine antagonists) or inhibitors of cytokine synthesis. Suitable other β_2-adrenoreceptor agonists include salmeterol (e.g. as the xinafoate), salbutamol (e.g. as the sulphate or the free base), formoterol (e.g. as the fumarate), fenoterol or terbutaline and salts thereof.

Suitable PDE4-specific inhibitors include any compound that is known to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not compounds which inhibit other members of the PDE family as well as PDE4. Generally it is preferred to use a PDE4 inhibitor which has an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity. For the purposes of this disclosure, the cAMP catalytic site which binds R and S rolipram with a low affinity is denominated the "low affinity" binding site (LPDE 4) and the other form of this catalytic site which binds rolipram with a high affinity is denominated the "high affinity" binding site (HPDE 4). This term "HPDE4" should not be confused with the term "hPDE4" which is used to denote human PDE4. A method for determining IC_{50}s ratios is set out in US patent 5,998,428 which is incorporated herein in full by reference as though set out herein. See also PCT application WO 00/51599 for an another description of said assay.

Suitable PDE4 inhibitors include those compounds which have a salutary therapeutic ratio, i.e., compounds which preferentially inhibit cAMP catalytic activity where the enzyme is in the form that binds rolipram with a low affinity, thereby reducing the side effects which apparently are linked to inhibiting the form which binds rolipram with a high affinity. Another way to state this is that the preferred compounds will have an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity.

A further refinement of this standard is that of one wherein the PDE4 inhibitor has an IC_{50} ratio of about 0.1 or greater; said ratio is the ratio of the IC_{50} value for competing with the binding of 1nM of [^{3}H]R-rolipram to a form of PDE4 which binds rolipram with a high affinity over the IC_{50} value for inhibiting the PDE4 catalytic activity of a form which binds rolipram with a low affinity using 1 μM[^{3}H]-cAMP as the substrate.

Most suitable PDE4 inhibitors are those which have an IC_{50} ratio of greater than 0.5, and particularly those compounds having a ratio of greater than 1.0. Preferred compounds are *cis* 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]; these are examples of compounds which bind preferentially to the low affinity binding site and which have an IC_{50} ratio of 0.1 or greater.

Other suitable medicament compounds include: *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also known as cilomalast) disclosed in U.S. patent 5,552,438and its salts, esters, pro-drugs or physical forms; AWD-12-281 from elbion (Hofgen, N. et al. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98; CAS reference No. 247584020-9); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa Hakko in WO99/16766; K-34 from Kyowa Hakko; V-11294A from Napp (Landells, L.J. et al. Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-23, Geneva) 1998] 1998, 12 (Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a pthalazinone (WO99/47505, the disclosure of which is hereby incorporated by reference) from Byk-Gulden; Pumafentrine, (-)-p-[(4*a*R*,10*b*S*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide which

is a mixed PDE3/PDE4 inhibitor which has been prepared and published on by Byk-Gulden, now Altana; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from Vernalis; or T-440 (Tanabe Seiyaku; Fuji, K. et al. J Pharmacol Exp Ther,1998, 284(1): 162), and T2585.

Suitable anticholinergic agents are those compounds that act as antagonists at the muscarinic receptor, in particular those compounds, which are antagonists of the M_1 and M_2 receptors. Exemplary compounds include the alkaloids of the belladonna plants as illustrated by the likes of atropine, scopolamine, homatropine, hyoscyamine; these compounds are normally administered as a salt, being tertiary amines.

Particularly suitable anticholinergics include ipratropium (e.g. as the bromide), sold under the name Atrovent, oxitropium (e.g. as the bromide) and tiotropium (e.g. as the bromide) (CAS-139404-48-1). Also of interest are: methantheline (CAS-53-46-3), propantheline bromide (CAS- 50-34-9), anisotropine methyl bromide or Valpin 50 (CAS- 80-50-2), clidinium bromide (Quarzan, CAS-3485-62-9), copyrrolate (Robinul), isopropamide iodide (CAS-71-81-8), mepenzolate bromide (U.S. patent 2,918,408), tridihexethyl chloride (Pathilone, CAS-4310-35-4), and hexocyclium methylsulfate (Tral, CAS-115-63-9). See also cyclopentolate hydrochloride (CAS-5870-29-1), tropicamide (CAS-1508-75-4), trihexyphenidyl hydrochloride (CAS-144-11-6), pirenzepine (CAS-29868-97-1), telenzepine (CAS-80880-90-9), AF-DX 116, or methoctramine, and the compounds disclosed in WO01/04118.

Suitable antihistamines (also referred to as H_1-receptor antagonists) include any one or more of the numerous antagonists known which inhibit H_1-receptors, and are safe for human use. All are reversible, competitive inhibitors of the interaction of histamine with H_1-receptors. Examples include ethanolamines, ethylenediamines, and alkylamines. In addition, other first generation antihistamines include those which can be characterized as based on piperizine and phenothiazines. Second generation antagonists, which are non-sedating, have a similar structure-activity

relationship in that they retain the core ethylene group (the alkylamines) or mimic the tertiary amine group with piperizine or piperidine. Exemplary antagonists are as follows:

Ethanolamines: carbinoxamine maleate, clemastine fumarate, diphenylhydramine hydrochloride, and dimenhydrinate.

Ethylenediamines: pyrilamine amleate, tripelennamine HCl, and tripelennamine citrate.

Alkylamines: chlropheniramine and its salts such as the maleate salt, and acrivastine.

Piperazines: hydroxyzine HCl, hydroxyzine pamoate, cyclizine HCl, cyclizine lactate, meclizine HCl, and cetirizine HCl.

Piperidines: Astemizole, levocabastine HCl, loratadine or its descarboethoxy analogue, and terfenadine and fexofenadine hydrochloride or another pharmaceutically acceptable salt.

Azelastine hydrochloride is yet another H_1 receptor antagonist which may be used in combination with a PDE4 inhibitor.

Particularly suitable anti-histamines include methapyrilene and loratadine.

Generally, medicament particles suitable for delivery to the bronchial or alveolar region of the lung have an aerodynamic diameter of less than 10 micrometers, preferably less than 6 micrometers. Other sized particles may be used if delivery to other portions of the respiratory tract is also desired, such as the nasal cavity, mouth or throat. The medicament may be delivered as pure drug, but suitably where in dry powder form medicaments are delivered together with excipients (carriers) which are suitable for inhalation. Suitable excipients include organic excipients such as polysaccharides (i.e. starch, cellulose and the like), lactose, glucose, mannitol, amino acids, and maltodextrins, and inorganic excipients such as calcium carbonate or sodium chloride. Lactose is a preferred excipient.

Particles of powdered medicament and/or excipient may be produced by conventional techniques, for example by micronisation, milling or sieving. Additionally, medicament and/or excipient powders may be engineered with particular densities, size ranges, or characteristics. Particles may comprise active agents, surfactants, wall forming materials, or other components considered desirable by those of ordinary skill.

The excipient may be included with the medicament via well-known methods, such as by admixing, co-precipitating and the like. Blends of excipients and drugs are typically formulated to allow the precise metering and dispersion of the blend into doses. A standard blend, for example, contains 13000 micrograms lactose mixed with 50 micrograms drug, yielding an excipient to drug ratio of 260:1. Dosage blends with excipient to drug ratios of from 100:1 to 1:1 may be used. At very low ratios of excipient to drug, however, the drug dose reproducibility may become more variable.

Inhaler devices herein are particularly suitable for dispensing medicament for the treatment of respiratory disorders such as disorders of the lungs and bronchial tracts including asthma and chronic obstructive pulmonary disorder (COPD). In another aspect, the inhaler devices are suitable for dispensing medicament for the treatment of a condition requiring treatment by the systemic circulation of medicament, for example migraine, diabetes, pain relief e.g. inhaled morphine.

The amount of any particular medicament compound or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. The medicaments for treatment of respiratory disorders herein may for example, be administered to a human patient by inhalation at a dose of from 0.0005mg to 10 mg, preferably 0.005mg to 0.5mg. The dose range for adult humans is generally from 0.0005 mg to 100mg per day and preferably 0.01 mg to 1mg per day.

It will be understood that the present disclosure is for the purpose of illustration only and the invention extends to modifications, variations and improvements thereto.

The application of which this description and claims form part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described therein. They may take the form of product, method or use claims and may include, by way of example and without limitation, one or more of the following claims:

Claims

1. A method for predicting the tendency of inhaled particles to deposit within a first patient's throat when said particles are inhaled through an airway defined by said throat, said method comprising

determining at least one internal physical parameter of said airway defined by the first throat by means of acoustic imaging of the airway defined by the first throat; and

matching said at least one internal physical parameter of the airway of the first throat with a dataset comprising pre-determined data relating to the corresponding internal physical parameter for the throat of at least one other patient,

wherein said dataset also comprises pre-determined data relating to the tendency of said inhaled particles to deposit within each of said at least one other patient's throat, and said matching thereby enables prediction of the tendency for the inhaled particles to deposit within the first patient's throat.

Abstract

There is provided a method for predicting the tendency of inhaled particles to deposit within a first patient's throat when said particles are inhaled through an airway defined by said throat. The method comprises determining at least one internal physical parameter of said airway defined by the first throat by means of acoustic imaging of the airway defined by the first throat; and matching said at least one internal physical parameter of the airway of the first throat with a dataset comprising pre-determined data relating to the corresponding internal physical parameter for the throat of at least one other patient, wherein said dataset also comprises pre-determined data relating to the tendency of said inhaled particles to deposit within said plural at least one other patient's throat, and said matching thereby enables prediction of the tendency for the inhaled particles to deposit within the first patient's throat.

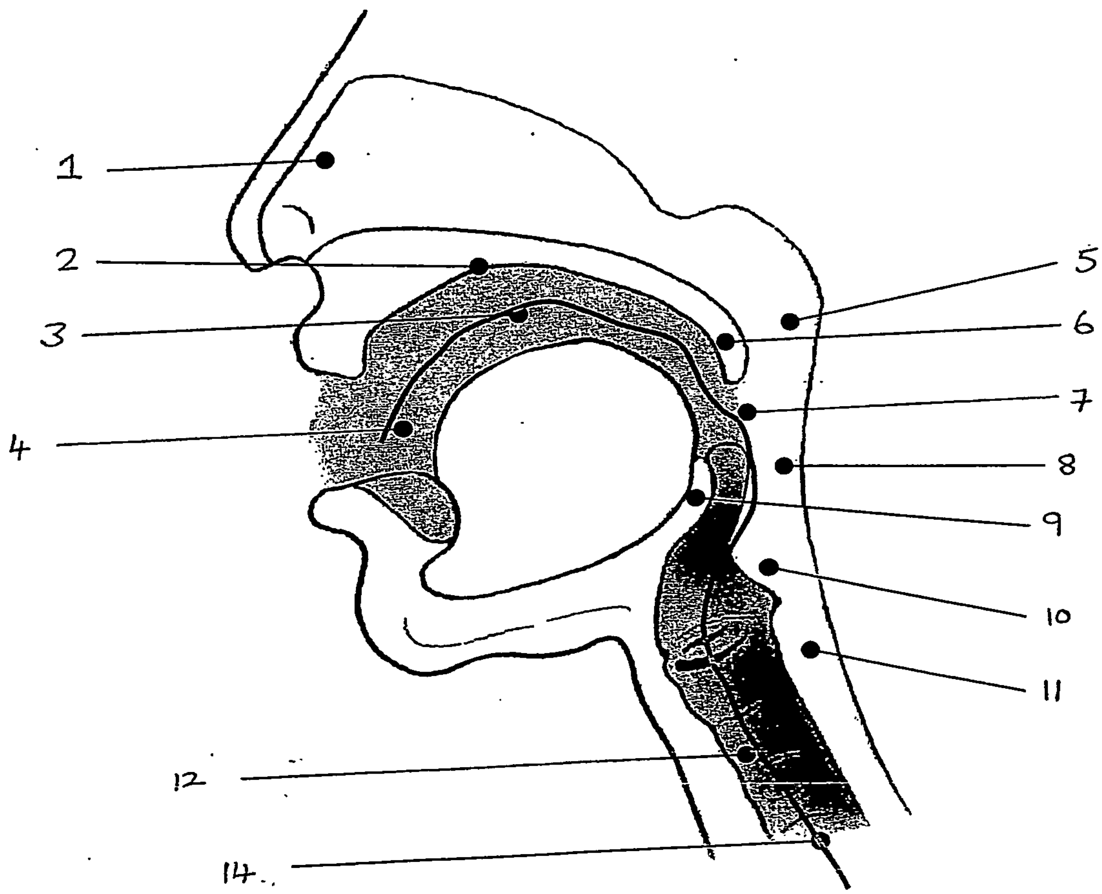

Figure 1

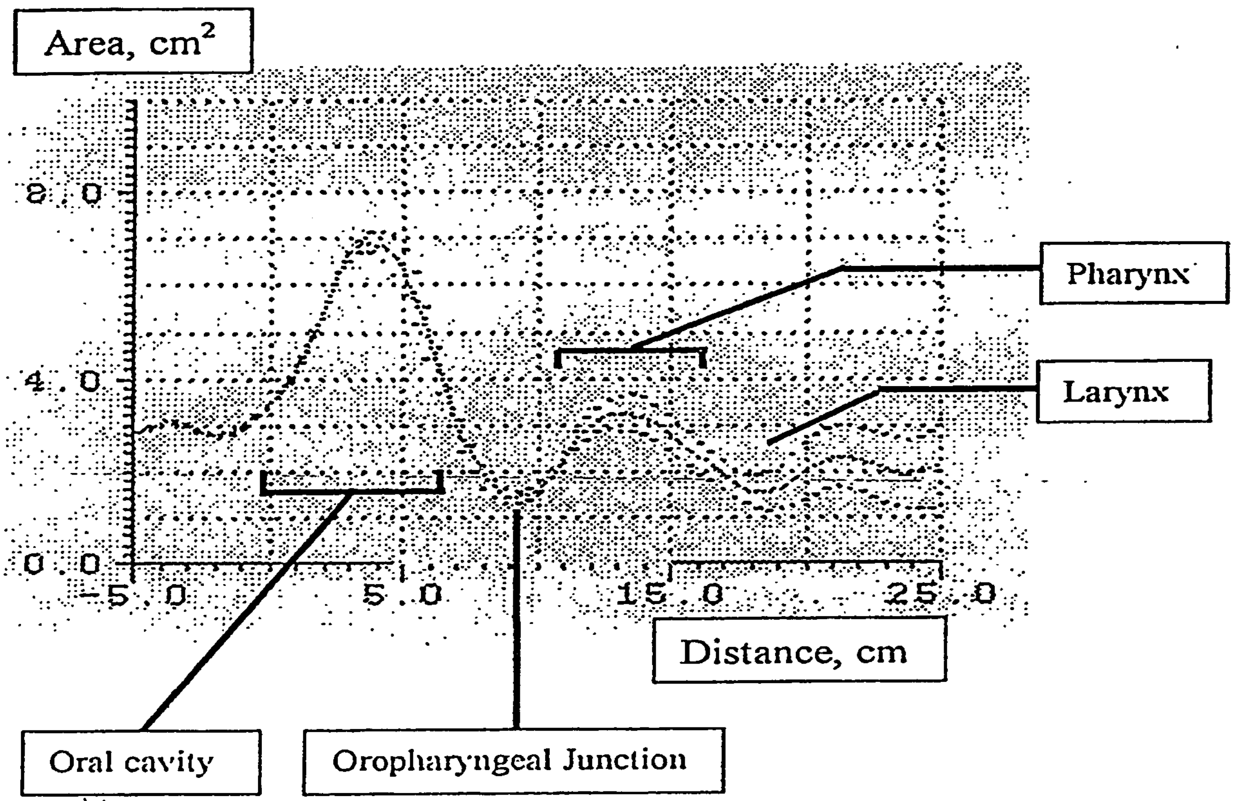
Area, cm²
8.0
4.0
0.0
-5.0
5.0
15.0
25.0
Distance, cm
Pharynx
Larynx
Oral cavity
Oropharyngeal Junction

Figure 2

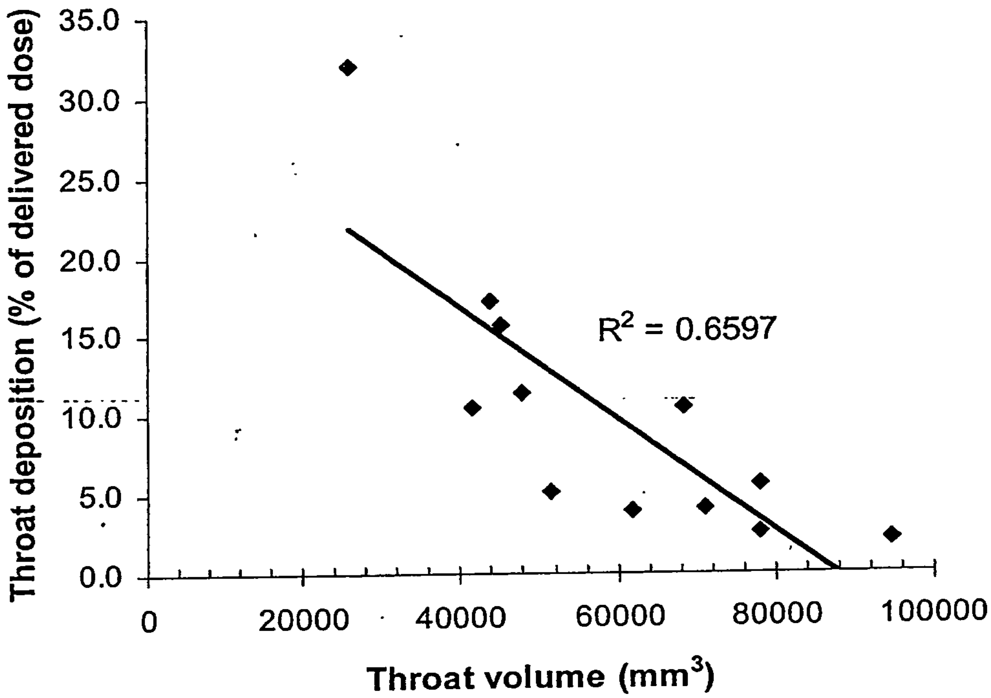
Throat deposition (% of delivered dose)
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
0
20000
40000
60000
80000
100000
Throat volume (mm3)
R2 = 0.6597

Figure 3

PCT/EP2004/014767 SPO